PATENT COOPERATION TREA

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
GOODWIN PROCTER LLP
Attn. Greenhalgh. Duncan A.
Exchange Place
53 State Street
Boston, MA 02109
UNITED STATES OF AMERICA

RECEIVED
JUL 07 2005
GOODWIN PROCTER LLP

Applicant's or agent's file reference RIB-030PC	Date of mailing (day/month/year) 06/07/2005
International application No. PCT/US2004/024339	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant RIB-X PHARMACEUTICALS, INC.	International filing date (day/month/year) 28/07/2004

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneve 20, Switzerland, Fascimile No.: (41–22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an International preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for International preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL–2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Federico Bonomelli

Form PCT/ISA/220 (January 2004) *(See notes on accompanying sheet)*

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
RIB-030PC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2004/024339	28/07/2004	29/07/2003
Applicant		
RIB-X PHARMACEUTICALS, INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to the Authority (Rule 23.1(b)).
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box II).

3. [ ] **Unity of invention is lacking** (see Box III).

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D263/20 C07D413/10 C07D413/12 C07D413/14 C07D417/10
C07D417/12 C07D417/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 352 781 A (E.I. DU PONT DE NEMOURS AND COMPANY) 31 January 1990 (1990-01-31) page 16, line 21 - page 17, line 2 page 31 - page 33; examples 65,67 -/--	1-6,10, 17-25, 29,30, 36-40, 44-47, 51-54, 56,57,60

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevence

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 June 2005	06/07/2005
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Fink, D

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 694 543 A (BAYER AG) 31 January 1996 (1996-01-31) page 13, line 42 - line 58 page 21 page 22, line 44 - line 50 page 49; example 36	1-6, 10-12, 14,15, 17-24, 29-31, 36-39, 44, 51-53, 56,57, 60-62, 64,65, 68,69
X	WO 03/022824 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; GRAVESTOCK, MICHAEL, BARRY; HA) 20 March 2003 (2003-03-20) page 24 - page 25 page 56; example 5	1-20,51, 52,54, 56-65, 68-89, 120,121, 123, 125-134, 137,138
A	GLEAVE D M ET AL.: "Synthesis And Antibacterial Activity of '6,5,5! and '6,6,5! Tricyclic Fused Oxazolidinones" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 8, no. 10, 19 May 1998 (1998-05-19), pages 1231-1236, XP004137053 page 1233; Scheme 3, step (b)	1-69
A	MOLANDER G A ET AL: "PALLADIUM-CATALYZED SUZUKI-MIYAURA CROSS-COUPLING REACTIONS OF POTASSIUM ARYL- AND HETEROARYLTRIFLUOROBORATES" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 68, no. 11, 30 May 2003 (2003-05-30), pages 4302-4314, XP001160394 ISSN: 0022-3263	1,55,70, 124
P,X	WO 2004/029066 A (RIB-X PHARMACEUTICALS, INC) 8 April 2004 (2004-04-08) page 236; Scheme 40 page 255; Scheme 49 page 291; Scheme 62 page 306; Scheme 69	1-69

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/048392 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; CARCANAGUE, DANIEL, ROBERT; GR) 10 June 2004 (2004-06-10) page 58, line 6 - page 60 pages 95-107; examples 13-21 page 109 - page 122; examples 25-30,33-36 page 125 - page 126; example 41 page 135 - page 144; examples 52,54,55 page 150 - page 165; examples 60-64	1-20,51, 52,54, 68-89, 120,121, 123, 125-134, 137,138
P,X	WO 2004/056817 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; GRAVESTOCK, MICHAEL, BARRY; HA) 8 July 2004 (2004-07-08) page 62 page 86; example 4 page 89 - page 90; example 5 page 92; example 6	1-3, 5-20,51, 52,54, 68-72, 74-89, 120,121, 123, 125-134, 137,138
E	WO 2004/078753 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; GRAVESTOCK, MICHAEL, BARRY; HA) 16 September 2004 (2004-09-16) page 23, line 25 - page 24, line 5 page 29, line 18 - line 23 page 31, line 8 - line 14 page 39; example 1 page 46 - page 49; examples 2-5 page 83; example 40	1-20, 51-54, 68-89, 120-123, 125-134, 137,138
E	WO 2005/012270 A (RIB-X PHARMACEUTICALS, INC; OYELERE, ADEGBOYEGA, K; GOLDBERG, JOEL, A;) 10 February 2005 (2005-02-10) page 47; Scheme 1 page 50, line 5 - line 6 page 52, line 13 - line 14 page 54; Scheme 10 page 56; Scheme 12	1-69
E	WO 2005/019211 A (RIB-X PHARMACEUTICALS, INC; ZHOU, JIACHENG; BHATTACHARJEE, ASHOKE; CHE) 3 March 2005 (2005-03-03) page 255 - page 258; claims 59-76 pages 24-27; Schemes A - D page 153; Scheme 1	1-138

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0352781	A	31-01-1990	US	4948801 A	14-08-1990
			AU	622465 B2	09-04-1992
			AU	3911589 A	01-02-1990
			CA	1337526 C	07-11-1995
			DK	374389 A	30-01-1990
			EP	0352781 A2	31-01-1990
			FI	893618 A	30-01-1990
			HU	58062 A2	28-01-1992
			IE	892438 L	29-01-1990
			JP	2124877 A	14-05-1990
			JP	2899319 B2	02-06-1999
			NO	893076 A	30-01-1990
			NZ	230108 A	25-10-1991
			PT	91315 A	08-02-1990
			US	5130316 A	14-07-1992
			US	5043443 A	27-08-1991
			US	5254577 A	19-10-1993
			ZA	8905778 A	27-03-1991
EP 0694543	A	31-01-1996	DE	4425612 A1	04-04-1996
			AU	699940 B2	17-12-1998
			AU	2498595 A	01-02-1996
			BG	99790 A	30-04-1996
			CA	2154025 A1	21-01-1996
			CN	1119647 A	03-04-1996
			CZ	9501872 A3	14-02-1996
			EE	9500045 A	15-02-1996
			EP	0694543 A1	31-01-1996
			FI	953477 A	21-01-1996
			HR	950408 A1	30-04-1997
			HU	75035 A2	28-03-1997
			IL	114626 A	17-08-1999
			JP	8041056 A	13-02-1996
			MA	23620 A1	01-04-1996
			NO	952865 A	22-01-1996
			NZ	272597 A	29-01-1997
			PL	309686 A1	22-01-1996
			RO	115262 B1	30-12-1999
			SG	33427 A1	18-10-1996
			SK	91795 A3	07-02-1996
			US	5627181 A	06-05-1997
			US	5843967 A	01-12-1998
			ZA	9506018 A	13-03-1996
WO 03022824	A	20-03-2003	BR	0212458 A	19-10-2004
			CA	2459766 A1	20-03-2003
			EP	1427711 A1	16-06-2004
			WO	03022824 A1	20-03-2003
			HU	0401005 A2	30-08-2004
			JP	2005507386 T	17-03-2005
			MX	PA04002303 A	29-06-2004
			US	2005107435 A1	19-05-2005
WO 2004029066	A	08-04-2004	AU	2003278995 A1	19-04-2004
			CA	2500158 A1	08-04-2004
			EP	1543017 A2	22-06-2005
			WO	2004029066 A2	08-04-2004

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 2004048392	A	10-06-2004	AU 2003302404 A1		18-06-2004
			WO 2004048392 A1		10-06-2004
WO 2004056817	A	08-07-2004	AU 2003292422 A1		14-07-2004
			WO 2004056817 A1		08-07-2004
WO 2004078753	A	16-09-2004	WO 2004078753 A1		16-09-2004
WO 2005012270	A	10-02-2005	US 2005043317 A1		24-02-2005
			WO 2005019211 A2		03-03-2005
			WO 2005012270 A2		10-02-2005
			WO 2005012271 A2		10-02-2005
WO 2005019211	A	03-03-2005	US 2005043317 A1		24-02-2005
			WO 2005019211 A2		03-03-2005
			WO 2005012270 A2		10-02-2005
			WO 2005012271 A2		10-02-2005

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/024339	28.07.2004	29.07.2003

International Patent Classification (IPC) or both national classification and IPC
C07D263/20, C07D413/10, C07D413/12, C07D413/14, C07D417/10, C07D417/12, C07D417/14

Applicant
RIB-X PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Fink, D

Telephone No. +49 89 2399-8701

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US2004/024339

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/024339

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	26-28,32-35,41-43,48-50,55,66,67,90-119,122,124,135,136
	No:	Claims	1-25,29-31,36-40, 44-47,51-54,56-65,68-89,120,121.123,125-134,137,138
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-138
Industrial applicability (IA)	Yes:	Claims	1-138
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item IV.

It is considered that the present application relates to **two** inventions which are not so linked as forming a single general inventive concept as set forth in Rule 13(1) PCT:

The prior art EP-A-0694543 (**D2**) discloses a process (cf., page 13, lines 42-58) for the preparation of 5-(acylaminomethyl)-3-bi(hetero)aryl-oxazolidin-2-ones (cf., claim 1) where a 5-(acylaminomethyl)-3-(halo(hetero)aryl)-oxazolidin-2-one of the general formula (If) is reacted with a (hetero)aryl boronic acid of the general formula (IX) (cf., the compound D'-R^{32}).
More specifically, **D2** teaches (cf., the example 36) the preparation of the compound (5S)-5-(Acetylaminomethyl)-3-[5-(4-methylphenyl)pyridin-2-yl)]-oxazolidin-2-one by the reaction of (5S)-5-(Acetylaminomethyl)-3-(5-bromopyridin-2-yl)]-oxazolidin-2-one with 4-methylphenyl boronic acid in THF/water in the presence of sodium carbonate and a tetrakis(triphenylphosphine) palladium catalyst.

The document WO-A-03/022824 (**D3**), on the other hand teaches a process (cf., pages 24-25; page 56, example 5) for the preparation of e.g. 5-(acylamino/oxymethyl)-3-blaryl-oxazolidin-2-ones (cf., claim 1) by reacting e.g. oxazolidin-2-on-3-ylaryl boronic acid derivative (such as the (5R)-[3-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-oxazolidin-2-on-5-yl]methyl acetate of the example 5) with an aryl halide (such as the [3-(4-bromophenyl)-4,5-dihydroisoxazol-5-yl]methanol of the example 5) in THF/water in the presence of potassium carbonate and a (palladium (II) acetate / 2-di-t-butylphosphinyl)biphenyl) catalyst.

In the light of this prior art **D2** and **D3**, the **problem** to be solved by the present application may be seen in the provision of further processes for the preparation of 3-bi(hetero)aryl-oxazolidin-2-ones.

Accordingly, the present application proposes the processes of the present independent **claims 1** and **70** in order to **solve** the given problem.

It appears, however, that the said solutions are not linked by a technical relationship involving a *special technical feature* (Rule 13.1 and 13.2 PCT):

The only technical features which are **common** to both of the present independent process **claims 1** and **70** are that

(i) a *borane* derivative (cf., the compound (I) of the present **claim 1** and the compound (II) of the present **claim 70**) is reacted with a *halo* or *sulfonate* derivative (cf., the compound (II) of the present **claim 1** and the compound (I) of the present **claim 70**)
(ii) in a *solvent* in the presence of
(iii) a *base* and
(iv) a *palladium* catalyst.

However, these features are already **known** from the prior art **D2** (see, for instance, the example 36) and **D3** (see, for instance, the example 5).

As the only technical features which are common to **both** of the present independent process **claims 1** and **70** - are **not novel**, they cannot represent the "special technical feature" within the meaning of Rule 13.2 PCT.

Hence the International Searching Authority considers that the two processes of the present **claims 1** (closest prior art **D2**) and **70** (closest prior art **D3**) represent separate inventions (or groups of inventions) which are not so linked as to form a single general inventive concept (Rule 13.1 PCT):

However, in order to facilitate the present examination procedure the following statement

on patentability is **complete** with respect to the present set of claims (i.e., **claims 1-138**)

Re Item V.

Reference is made to the following documents:

D1: ..... EP-A-0352781 (31 January 1990);
D2: ..... EP-A-0694543 (31 January 1996);
D3: ..... WO-A-03/022824 (20 March 2003);
D4: ..... *Bioorganic & Medicinal Chemistry Letters* **8**(10), 1231-1236 (19 May 1998);
D5: ..... *Journal of Organic Chemistry* **68**(11), 4302-4314 (30 May 2003);
D6: ..... WO-A-2004/029066 (***8 April 2004***);
D7: ..... WO-A-2004/048392 (***10 June 2004***);
D8: ..... WO-A-2004/056817 (***8 July 2004***);
D9: ..... WO-A-2004/078753 (***16 September 2004***);
D10: ..... WO-A-2005/012270 (***10 February 2005***);
D11: ..... WO-A-2005/019211 (***3 March 2005***);

The current assessment is based on the assumption that all claims enjoy priority rights from the filing date (*29 July 2003*) of the priority document *US 60/490,855*.
If it later turns out that this is not correct, the documents **D6 - D11** as cited in the International Search Report could become relevant.

1. NOVELTY (Article 33(2) PCT):

The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of **claims 1-25, 29-31, 36-40, 44-47, 51-54, 56-65, 68-89, 120, 121, 123, 125-134, 137** and **138** is **not** new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT):

There is an overlap between the process as detailed on page 16, line 21 - page 17, line 2 of **D1** (in combination with claim 1 of **D1**) and the present process **claims 1-6, 10, 17-25, 29, 30, 36-40, 44-47, 51-54, 56, 57** and **60**.

Moreover, **D1** discloses two specific examples (cf., the examples 65 and 67) falling within the said range of overlap.
Accordingly, the **whole** range of overlap is considered to be novelty-destroying (Article 33(2) PCT).

The same observation applies in the case of the prior art **D2**. There is an overlap with the process of **D2** (cf., page 13, lines 42-58) and the present **claims 1-6, 10-12, 14, 15, 17-24, 29, 30, 31, 36-39, 44, 51-53, 56, 57, 60-62, 64, 65, 68** and **69**.
D2 also discloses a specific example falling within the said range of overlap (cf., page 49, example 36).
Again, the **whole** range of overlap is considered to be novelty-destroying (Article 33(2) PCT).

Furthermore, there is an overlap between the process of **D3** (cf., pages 24-25 in combination with claim 1) and the present process **claims 1-20, 51, 52, 54, 56-65, 68-89, 120, 121, 123, 125-134, 137** and **138**.
Moreover, **D3** discloses a specific example falling within the said range of overlap (cf., page 56, example 5).
Again, the **whole** range of overlap is considered to be novelty-destroying (Article 33(2) PCT).

The document **D4** describes (cf., page 1233; Scheme 3, step b) the Suzuki palladium-catalysed cross-coupling ($(Ph_3P)_4Pd$ / $KHPO_4$) of some ***[6,5,5] tricyclic*** oxazolidinones.
The processes of the present **claims 1-138** for the preparation of 3-aryl-oxazolidinones are thus novel over **D4** (the present groups B and Het may not together form a *tricyclic*

oxazolidinone).

Document **D5** does **not** relate to the preparation of compounds comprising the present *heterocyclic group* ***Het*** (cf., the definition of *Het* according to the present claims 1 and 70). The present **claims 1-138** are therefore also novel over **D5**.

2. INVENTIVE STEP (Article 33(3) PCT):

The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of **claims 1-138 - as far as it is novel** (see, item 1 above) does not involve an inventive step (Rule 65(1)(2) PCT):

2.1. Document **D2** - which is considered to represent the **closest prior art** with respect to the present **claims 1-69** - teaches a process (cf., page 13, lines 42-58) for the preparation of 5-(acylaminomethyl)-3-bi(hetero)aryl-oxazolidin-2-ones (cf., claim 1) where a 5-(acylaminomethyl)-3-(***halo***(hetero)aryl)-oxazolidin-2-one of the general formula (If) is reacted with a (hetero)aryl ***boronic acid*** of the general formula (IX) (cf., the compound D'-R^{3c}).
More specifically, **D2** teaches (cf., the example 36) the preparation of the compound (5S)-5-(Acetylaminomethyl)-3-[5-(4-methylphenyl)pyridin-2-yl)]-oxazolidin-2-one by the reaction of (5S)-5-(Acetylaminomethyl)-3-(5-***bromo***-pyridin-2-yl)]-oxazolidin-2-one with 4-methylphenyl ***boronic acid*** in ***THF / water*** in the presence of ***sodium carbonate*** and ***a tetrakis(triphenylphosphine) palladium*** catalyst.

The said process of **D2** is considered to be novelty-destroying in respect of the present **claims 1-6, 10-12, 14, 15, 17-24, 29-31, 36-39, 44, 51-53, 56, 57, 60-62, 64, 65, 68** and **69** (see item 1 above).

In the light of the prior art **D2**, the **problem** underlying the present application resides

in the provision of a **further** process for the preparation of 3-bi(hetero)-aryl-oxazolidin-2-ones of the present general formula of **claim 1**.

This problem has been **solved** by the process of the present **claims 1-69** (cf., the present working examples).

The present solution - **as far as it is novel** - cannot, however, be considered to involve an inventive step for the following reasons:

The present dependent process **claims 26-28, 32-35, 41-43, 48-50, 55, 66** and **67** - which may be regarded to be **novel** over **D1 - D3** - cannot be considered to involve an inventive step because they concern either

(i) the preparation of specifically preferred compounds of the present general formula (cf., the present dependent **claims 27, 28, 32-35, 42, 43** and **48-50**), the preparation of which appears to be obvious in the light of the teachings of **D2** and/or **D1** and **D3** (given (i) the broad applicability of the Palladium-catalysed Suzuki cross-coupling reaction and (ii) the fact that this method has been already successfully applied to a wide variety of *structurally related* 3-biaryl-oxazolidin-2-ones (cf., **D1 - D3**), the skilled person would have **expected** that the Suzuki cross-coupling methods of **D1 - D3** would also be suitable for the synthesis of the compounds of the present dependent **claims 27, 28, 32-35, 42, 43** and **48-50**), or

(ii) process features (cf., the present dependent **claims 26, 41, 55, 66** and **67**) which are either (i) obvious per se (cf., the *removal of amine protecting groups* according to the present **claims 26** and **41**; or the use of the *potassium trifluoroborate* according to the present **claim 55** (which is a known *equivalent* of the *boronic acid* residue (cf.,, **D5**))), or
(ii) have to be regarded as obvious modifications of the reaction conditions of e.g. **D2** (the solvent mixture *water / toluene / ethanol* of the present **claim 66** is already suggested by **D2** (see, page 21, last paragraph ("...*ethanol*,.....*toluene*,.....*mixtures* of the said solvents..."); page 22, lines 44-45; and the example 36 (cf., the "...*2M* Na_2CO_3..."); and the *specific*

water / toluene / ethanol *ratio 1:3:1* according to the present **claim 67** is considered to merely represent the result of an optimization of solvent conditions which is a routine task of the person skilled in the art).

2.2. Document **D3** - which is considered to represent the **closest prior art** with respect to the present **claims 70-138** - teaches a process (cf., pages 24-25; page 56, example 5) for the preparation of e.g. 5-(acylamino/oxymethyl)-3-biaryl-oxazolidin-2-ones (cf., claim 1) by reacting e.g. oxazolidin-2-on-3-ylaryl ***boronic acid*** derivative (such as the (5R)-[3-[3-fluoro-4-(***4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl***)phenyl]-oxazolidin-2-on-5-yl]methyl acetate of the example 5) with an aryl ***halide*** (such as the [3-(4-***bromo***phenyl)-4,5-dihydroisoxazol-5-yl]methanol of the example 5) in a *solvent* (such as ***THF*** / ***water*** in the example 5) in the presence of a *base* (such as ***potassium carbonate*** in the example 5) and a *palladium* catalyst (such as ***palladium*** (II) acetate / ***2-(di-t-butylphosphinyl)-biphenyl*** in the example 5). The said process of **D3** is considered to be novelty-destroying in respect of the present **claims 70-89, 120, 121, 123, 125-134, 137** and **138** (see item 1 above).

In the light of the prior art **D3**, the **problem** underlying the present application resides in the provision of a **further** process for the preparation of 3-bi(hetero)-aryl-oxazolidin-2-ones of the present general formula of **claim 70.**

This problem has been **solved** by the process **of** the present **claims 70-138** (cf., the present working examples).

The present solution - **as far as it is novel** - cannot, however, be considered to involve an inventive step for the following reasons:

Again, the present dependent process **claims 90-119, 122, 124, 135** and **136** - which may be regarded to be **novel** over **D3** - cannot be considered to involve an inventive step because they merely concern either

(i) the preparation of specifically preferred compounds of the present general formula (cf., the present dependent **claims 90-94, 96-109** and **111-119**), the

preparation of which appears to be obvious in the light of the teachings of **D3** and/or **D1** and **D2** (given (i) the broad applicability of the Palladium-catalysed Suzuki cross-coupling reaction and (ii) the fact that this method has been already successfully applied to a wide variety of *structurally related* 3-biaryl-oxazolidin-2-ones (cf., **D1** - **D3**), the skilled person would have **expected** that the Suzuki cross-coupling methods of **D1** - **D3** would also be suitable for the synthesis of the compounds of the present dependent **claims 90-94, 96-109** and **111-119**), or

(ii) process features (cf., the present dependent **claims 26, 41, 55, 66** and **67**) which are either (i) obvious per se (cf., the *removal of amine protecting groups* according to the present **claims 95** and **110**; the use of the *boronic acid* according to **claim 122** (*boronic acids* and *boronic acid esters* are known to be equally useful in the Palladium-catalysed Suzuki cross-coupling reaction (cf., for example, **D5**: page 4302, column 2, last paragraph - page 4303, column 1 , line 7)); or the use of the *potassium trifluoroborate* according to the present **claim 124** (which is a known *equivalent* of the *boronic acid* residue (cf.,, **D5**))), or
(ii) have to be regarded as obvious modifications of the reaction conditions of e.g. **D2** (the solvent mixture *water / toluene / ethanol* of the present **claim 135** is already suggested by **D2** (see, page 21, last paragraph ("...*ethanol*,.....*toluene*,.....*mixtures* of the said solvents..."); page 22, lines 44-45; and the example 36 (cf., the "...*2M* Na_2CO_3...")); and the *specific* water / toluene / ethanol *ratio 1:3:1* according to the present **claim 136** is considered to merely represent the result of an optimization of solvent conditions which is a routine task of the person skilled in the art).

2.3. Accordingly, it is considered that - in the absence of any **unexpected** and/or **surprising effects** - the subject-matter of the present **claims 1-138 - as far as it is novel** - has to be regarded to be **obvious** in the light of the prior art **D1** - **D3** and **D5** (Article 33(3) PCT).

3. INDUSTRIAL APPLICABILITY (Article 33(4) PCT):

The subject-matter of the present **claims 1-138** concerns chemical processes and is therefore considered to be industrial applicable in the sense of Article 33(4) PCT.

4. MISCELLANEOUS:

4.1. The documents **D1 - D5** should have been cited (Rule 5.1(a)(ii) PCT).

4.2. Claims 2, 3, 71 and 72 - which are drafted as independent process claims - comprise all the features of independent process claims 1 and 70 and are therefore not appropriately formulated as claims dependent on claim 1 and claim 70, respectively (Rule 6.4 PCT).

4.3. The expression "amine protecting group" (cf., the present claims 24-26, 39-41, 93-95 and 108-110) is considered to be unclear in the sense of Article 6 PCT. This expression is a functional definition which does not comprise any information as regards the *structure* of the respective compounds.

4.4. The use of the relative term "about" (cf. the present claims 59, 63, 67, 68, 128, 132, 136 and 137) should be avoided because it leaves the skilled person in doubt as to the lower and the upper limits of the given ranges, thus rendering the scope of the said claims unclear (Article 6 PCT).

4.5. The passages of the present description referring (i) to Z as "...an *electronegative substituent*..." (cf., page 3, line 13; page 4, line 5; and page 9, line 30) and (ii) to "*N-oxide*", "*N-hydroxy*" and "*N-alkoxy*" derivatives of the "claimed nitrogen-containing compounds" (cf., page 6, first paragraph) create an inconsistency between the claims and the description (according to claims 1 and 70, the group Z is **only**

selected from *I*, *Br*, *Cl*, and $R^9OSO_3^-$, and the present claims do **not** comprise any information in respect of the said "*N-oxide*", "*N-hydroxy*" and "*N-alkoxy*" derivatives), which leads to a doubt concerning the extent of protection afforded by the claims, thus rendering the claims unclear (Article 6 PCT).

4.6. The statements on pages 1 (line 6) and 82 (lines 9-16), concerning (i) the incorporation of patent applications, patent documents and scientific articles and (ii) the scope of the present invention are obviously irrelevant and unnecessary in the sense of Rule 9.1(iv) PCT.